REMARKS

Applicants respectfully request reconsideration of this application in view of the following remarks.

Upon entry of this Amendment, claims 1-21 and 23-25 will be pending in this application. Claim 22 was canceled because it is duplicative of amended claim 20. Claim 2 was amended to recite that the EBV antigen can be EBNA1 or EBNA2. Pursuant to 37 C.F.R. § 1.73(c), support for this amendment can be found in the specification, including, for example, at Col. 9, lines 9-32. Claims 4, 6, 9, 12, 15 and 20 have been amended to change their dependency from claim 1 to claim 2. This Amendment does not introduce any new matter.

Applicants also submit that this Amendment does not raise new issues or necessitate the undertaking of any additional search of the art by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. Therefore, this Amendment should allow for immediate action by the Examiner.

Applicants respectfully request that this Amendment be entered by the Examiner, placing claims 1-21 and 23-25 in condition for allowance, or in better form for appeal, should the Examiner dispute the patentability of the pending claims.

Specification

The Office objected to the specification because the first paragraph did not include the cross-reference information establishing the relationship between this

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reissue application the issued patent. (Paper No. 9, p. 2.) Applicants have amended the first paragraph of this reissue application to include the requested cross-reference information.

Rejections Under 35 U.S.C. § 112, First Paragraph

1. Written Description

The Office rejected claims 1-16 and 20-25 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (Paper No. 9, p. 2.) The Office notes that the claims read on a genus of promoters whose transcriptional activity is activated by an Epstein-Barr Virus ("EBV") antigen or a papilloma virus antigen. *Id.* Without presenting any evidence or reasons, however, the Office asserts that "the specification . . . provides sufficient description of only one species of the chimeric promoter EBNA1-RE/TP1 (column 7)." *Id.* Applicants respectfully traverse this rejection.

The PTO has the initial burden of presenting evidence or reasons why those skilled in the art would not recognize in the specification a description of the invention defined by the present claims. *In re Voss*, 194 U.S.P.Q. 267, 271 (C.C.P.A. 1977); M.P.E.P. § 2163.04. The specification clearly describes the invention as claimed. For example, in describing how to target the expression of the heterologous sequence in the adenovirus to tumor cells, the specification explains:

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> As indicated above, the heterologous DNA sequence is placed under the control of expression signals which are active specifically in tumour cells. In this way, the gene used is expressed and produces its effect only when the virus has indeed infected a tumour cell.
>
> In a preferred embodiment of the invention, they are expression signals which are induced by or active in the presence of viruses responsible for or associated with tumours. Still more preferably, an expression signal inducible by the Epstein-Barr virus (EBV) or by the papilloma virus is used within the framework of the present invention.

(Col. 4, lines 27-37.)

The specification further explains that EBV is associated with Burkitt's lymphoma and cancer of the nasopharnyx and that papilloma viruses are associated with cervical cancer. Col. 4, line 38 through Col. 5, line 3. In biopsies of nasopharnyx cancer, the EBV antigen, EBNA1, is regularly present. Col. 4, lines 44-45. And the human papilloma virus (HPV) antigen, E6, leads to tumor formation in HPV-infected cells by decreasing the levels of the tumor suppressor gene p53. Col. 4, lines 62-65. In addition, the specification provides a working example showing that EBNA1 and EBNA2 stimulate expression of a heterologous sequence placed under the control of an expression signal that is inducible by an EBV antigen. Thus, given applicants' disclosure, one of skill in the art would understand that any promoter sequence that is inducible by an EBV antigen or by a papilloma virus antigen could be used in applicants' claimed adenovirus to target heterologous gene expression to a cell that expresses an EBV or papilloma virus antigen.

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In maintaining the written description rejection, the Office asserts that "the evidentiary support for the lack of sufficient description of a representative number of species of the genus of EBV inducible promoters or a papilloma virus antigen-inducible promoters [sic, promoter] is the fact that the as-filed specification only describes one species of a chimeric promoter, which composed mainly of the EBNA1 response element (EBNA1-RE) fused upstream of a viral promoter." (Paper No. 9. p. 5.) The specification, however, discloses more than a single chimeric promoter. For example, the specification discloses that EBNA1 transactivates the viral promoter BCR2[1] (as recited in claim 25) and the EBNA1 response element[2] (as recited in claim 17). It also discloses that the EBNA1 response element can be fused with other promoter sequences, such as the TP1 promoter, to form a chimeric promoter. Thus, the specification's disclosure is not limited to a single chimeric promoter.

Furthermore, a specification need not disclose what is conventional or well known to one of ordinary skill in the art. *See* M.P.E.P. § 2163, p. 2100-166. Here, the existence of promoter sequences responsive to EBV antigens or to papilloma virus antigens were well known in the art. For example, as of the original filing date of the instant application,[3] the E6 protein of human papilloma virus (HPV) was known to activate various promoter sequences, including numerous heterologous promoter sequences, such as the promoter of the herpes simplex virus thymidine kinase gene, the human immunodeficiency virus long terminal repeat sequence, adenovirus major

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1 Col. 4, lines 44-48.
2 Col. 4, lines 48-58; Col. 7, line 29-40.
3 French priority application FR 93/13766 was filed November 18, 1993.

late promoter, adenovirus E2 promoter, HPV-16 p97, and SV40 early promoter.[4] All of these promoter sequences contain a TATA motif, demonstrating a correlation between function and structure. (Desaintes et al., p. 329, paragraph spanning Col. 1 and Col. 2.) Desaintes et al. also found that E6 could induce transcription from various mutant forms of the heterologous promoters identified above, showing that one of skill in the art would appreciate how to modify a wild type promoter sequences to obtain a promoter sequences that differed in sequence from the wild type promoter and yet still retained the ability to promote transcription. (Desaintes et al., pp. 329-31.) Thus, as of November 18, 1993, one of ordinary skill in the art would have recognized that E6 is capable of activating numerous promoter sequences, particularly those containing a TATA sequence.

Regarding EBV antigens, as of the original filing date of this application, EBNA2, was known to transcriptionally activate cellular genes (e.g., CD 21, CD23, and c-*fgr*), as well as EBV genes (e.g., LMP, TP1, and TP2).[5] Zimber-Strobl et al. identified an EBNA2 responsive region between -177 and -258 (relative to the *TP1* cap site), which contained a consensus sequence also found in the LMP, BamHI-C,[6] and CD23 promoters. (Zimber-Strobl et al., p. 169.) EBNA2 was also known to transactivate the

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[4] Desaintes et al., *Transcriptional Activation of Several Heterologous Promoters by the E6 Protein of Human Papillomavirus Type 16*, Journal of Virology, 66(1):325-33 (1992) (Exhibit 1).

[5] Zimber-Strobl et al., *The Epstein-Barr Virus Nuclear Antigen 2 Interacts with an EBNA2 Responsive Cis-Element of the Terminal Protein 1 Gene Promoter*, The EMBO Journal, 12(1):167-75 (1993) (Exhibit 2).

[6] BamHI C is an endogenous EBV promoter. Sung et al., *EBNA-2 Transactivates a Lymphoid-Specific Enhancer in the BamHI C Promoter of Epstein-Barr Virus*, Journal of Virology, 65(5):2164-69 (1991). (Exhibit 3)

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long terminal repeat of the human immunodeficiency virus.[7] As disclosed in the specification, EBNA1 transactivates the EBNA responsive element of EBV. EBNA1 has also been shown to bind to a DNA having the following partial palindromic nucleotide sequence: TAGGATAGCATATGCTACCCAGATCCAG, demonstrating a correlation between structure and function.[8]

Therefore, as of applicants' filing date, it was known that EBV and papilloma virus antigens, such as E6, EBNA2, and EBNA1, can activate numerous promoter sequences. Given this knowledge, the skilled artisan would have recognized that applicants' invention could be practiced with any promoter sequence that is inducible by an EBV antigen or by a papilloma virus antigen, including those promoter sequences discussed above, as well as variations thereof that retained the desired promoter activity. Applicants did not have to disclose in their specification what was already conventional in the art. "If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then adequate description requirement is met." (M.P.E.P. § 2163, p. 2100-166.) Such is the case here.

The Office notes that the claims encompass a genus of promoters that are inducible by an EBV antigen or a papillomavirus antigen. (Paper No. 2, p. 3.) In claims 2-23 and 25, the claimed adenovirus contains an expression signal that is activated by

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7 Scala et al., *Epstein-Barr Virus Nuclear Antigen 2 Transactivates the Long Terminal Repeat of Human Immunodeficiency Virus Type 1*, Journal of Virology, 67(5):2853-61 (May 1993). (Exhibit 4)

8 Kieff et al., *Epstein-Barr Virus and Its Replication*, in Fundamental Virology, 2nd Ed., p. 904 (Bernard N. Fields et al. eds. 1991). (Exhibit 5)

the EBNA1 or EBNA2 antigen, and in claims 20-23, the expression signal is a promoter sequence from EBV. In claim 24, the expression signal is activated by E6. The written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed invention. (*See* M.P.E.P. § 2163, p. 2100-164.) As discussed above, there were known correlations between promoter function and promoter structure. For example, the E6 protein was known to activate promoter sequences containing a TATA sequence. In other words, the chemical structure of the TATA sequence correlated with E6-induced promoter function. Similarly, as discussed above, the EBNA2-responsive region between -177 and -258 contains a consensus sequence that can be found in other EBNA2-inducible promoters. And EBNA1 can recognize a partial palindromic nucleotide sequence. Thus, as of applicants' filing date known correlations existed between the structure and function of the claimed promoter sequences. Accordingly, applicants have adequately described their claimed invention by combining both structural and functional characteristics.

The Office has provided no reasons to show why a person skilled in the art would not recognize in the specification a description of the invention defined by the present claims. Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 112, first paragraph, rejection.

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2. Enablement

The Office also rejected claims 1-16 and 20-25 under 35 U.S.C. § 112, first paragraph, asserting that the specification does not enable a person skilled in the art to make and use the invention commensurate in scope with the claimed invention. (Paper No. 5, p. 4.) The Office acknowledged that the specification enables a claim directed to:

> A replication defective recombinant adenovirus comprising a heterologous DNA sequence under the control of the chimeric promoter EBNA1-RE/TP1 which is inducible by an Epstein-Barr virus antigen or by a papilloma virus antigen.

Id. But the Office asserts that the specification is not enabling for other claimed embodiments. *Id.* Applicants respectfully traverse this rejection.

The Office has the initial burden of establishing a *prima facie* case of lack of enablement. (M.P.E.P. § 2164.04.) Applicants' specification disclosing how to make and use the claimed invention must be taken as complying with 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of the disclosure. *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1437, 1442 (Fed. Cir. 1995). The Office has questioned the scope of enablement provided by applicants' specification but has not given any technical reasons to support the rejection. And although the Office lists the eight *Wand* factors (*see* M.P.E.P. § 2164.01(a)), the Office provides no meaningful analysis of these factors with respect to the presently pending claims. As stated in *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971)(emphasis in original):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure

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> and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Thus, the PTO has not met its initial burden of establishing a *prima facie* case of lack of enablement.

In maintaining the enablement rejection, the Office asserts that:

> In view of the lack of written description for claiming a genus of expression signal sequences as claimed, the examiner maintains the lack of a sufficient description as set forth above, which leads to the lack of sufficient guidance and/or working examples to enable the full breadth of the claimed invention, a person skilled in the art, including those having a relatively high skill in the art of recombinant vectors, would not know how to make and use, without undue experimentation, the claimed invention as broadly claimed. As such, the examiner has provided sufficient evidence to show that the Wand Factors other than the relatively high skill [sic, of] those skilled in the art have not been met by the as-filed application.

(Paper No. 9, p. 6.)

In other words, the Office appears to argue that one of ordinary skill in the art would not know how to make and use the claimed invention without undue experimentation because of the allegedly insufficient written description. However, it is well settled that written description and enablement are separate and distinct requirements of 35 U.S.C. § 112, first paragraph. (M.P.E.P. § 2161.) It is improper to conclude that claims are not enabled because they lack adequate written description support. The legal standards for written description and enablement are not the same. Moreover, for the reasons discussed above, the specification provides adequate written description support for the pending claims.

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As discussed above, as of applicants' filing date, it was well known that EBV and papilloma virus antigens, such as EBNA1, EBNA2, and E6, could activate various cellular and viral promoter sequences, as well as variants thereof. In addition, there were known correlations between promoter function and promoter structure that would direct one of skill in the art to sequences that could be used in the claimed invention. The Office has offered no evidence that it would require undue experimentation for one of skill in the art to make and use the claimed invention using these known sequences or variants thereof. In the absence of such evidence, applicants respectfully request that the Office reconsider and withdraw this 35 U.S.C. § 112, first paragraph, rejection.

CONCLUSION

In view of the foregoing remarks, applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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Dated: September 8, 2003

By: _____
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EXPEDITED PROCEDURE
RESPONSE UNDER 37 C.F.R. § 1.116
GROUP ART UNIT: 1632

STATUS OF CLAIMS PURSUANT TO 37 C.F.R. § 1.173(c)

Upon entry of this Amendment, the status of the claims will be as follows:

1. (Pending) A replication defective recombinant adenovirus comprising a heterologous DNA sequence under the control of an expression signal which is inducible by an Epstein-Barr virus (EBV) antigen or by a papilloma virus antigen.

2. (Pending) The adenovirus according to claim 2, wherein the EBV antigen is EBNA 1.

3. (Pending) The adenovirus according to claim 2, wherein the expression signal consists of a chimeric promoter comprising a sequence which is activated by EBNA 1 antigen fused upstream of a viral promoter.

4. (Pending) The adenovirus according to claim 2, lacking regions of its genome which are required for replication in a target cell.

5. (Pending) The adenovirus according to claim 4, wherein said adenovirus is a type Ad5 human adenovirus or a type CAV-2 canine adenovirus.

6. (Pending) The adenovirus according to claim 2, wherein the heterologous DNA sequence comprises a gene which encodes a product toxic in a cell infected by said adenovirus.

7. (Pending) The adenovirus according to claim 6, wherein said product renders said cell sensitive to a therapeutic agent.

8. (Pending) The adenovirus according to claim 7, wherein the gene is the thymidine kinase gene and the therapeutic agent is ganciclovir or acyclovir.

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9. (Pending) The adenovirus according to claim 2, wherein the heterologous DNA sequence comprises a gene which encodes a product effective to inhibit cell division.

10. (Pending) The adenovirus according to claim 9, wherein the gene is selected from the group consisting of tumour suppressor genes, antisense sequences and ribozymes.

11. (Pending) The adenovirus according to claim 6, wherein the heterologous DNA sequence comprises a gene whose expression product induces apoptosis of a cell infected by said adenovirus.

12. (Pending) A composition comprising the replication defective recombinant adenovirus according to claim 2 and an acceptable carrier.

13. (Pending) The composition according to claim 12, in injectable form.

14. (Pending) The adenovirus of claim 3, wherein the viral promoter is the terminal protein 1 (TP1) gene promoter.

15. (Pending) An isolated cell comprising the adenovirus of claim 2.

16. (Pending) The composition of claim 12 comprising from 10^6 to 10^{10} pfu/ml of replication defective recombinant adenoviruses.

17. (Pending) The adenovirus according to claim 2, wherein the sequence which is activated by EBNA 1 antigen is the EBNA1 responsive element (EBNA1-RE).

18. (Pending) The adenovirus according to claim 14, wherein the sequence which is activated by EBNA 1 antigen is the EBNA1 responsive element (EBNA1-RE).

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19. (Pending) The adenovirus according to claim 17, wherein said adenovirus is a type Ad5 human adenovirus or a type CAV-2 canine adenovirus.

20. (Pending) The adenovirus of claim 2, wherein the expression signal comprises a promoter sequence from an Epstein-Barr virus.

21. (Pending) The adenovirus according to claim 20, wherein said adenovirus is a type Ad5 human adenovirus or a type CAV-2 canine adenovirus.

22. (Canceled) The adenovirus according to claim 20, wherein the promoter sequence is from an Epstein-Barr virus.

23. (Pending) The adenovirus according to claim 22, wherein the promoter sequence is inducible by EBNA1.

24. (Pending) The adenovirus according to claim 1, wherein the papilloma virus antigen is E6.

25. (Pending) The adenovirus according to claim 2, wherein the expression signal comprises a BCR2 viral promoter.

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